REMARKS

Claims 1, 4-7 and 11-18 are pending in the subject application. Claims 11-17 are withdrawn from consideration as being drawn to non-elected inventions. Applicants have hereinabove amended claim 1 and canceled claims 3-7 and 18 without disclaimer or prejudice to applicants' right to pursue the subject matter of these claims in the future. Support for the amendment to claim 1 may be found in the specification, *inter alia*, at page 2, lines 6-13 as well as in the Examples, for example at page 13, lines 1-19; page 15, last paragraph, 1st setences; page 19, middle paragraph . 1st sentence and original claim 4. Applicants have added new claim 19. Support for new claim 19 may be found in the specification, *inter alia*, at page 3, lines 8-11 and in the Examples, for example at page 11, 1st sentence. Upon entry of this Amendment, claims 1 and 19 will be pending and under examination.

Information Disclosure Statement

Applicants acknowledge that the Examiner, on page 3 of the Final Office Action, has considered all the references listed in the Information Disclosure Statement filed May 6, 2008 except for EP1172378 since it was cited by the Examiner on form PTO 892 mailed May 3, 2007.

Withdrawn Rejections

Applicants note that the Examiner has withdrawn, on page 3 of the December 23, 2008 Final Office Action, the rejection of claims 1, 3-7 and 18 under 35 U.S.C. §112, second paragraph, as being indefinite.

Rejection Under 35 U.S.C. §112

The Examiner rejected claim 1, 4-7 and 18 under 35 U.S.C. §112, first paragraph, for allegedly failing to satisfy the enablement requirement. Specifically, in section 7 at page 4 of the Final Office Action, the Examiner states that "Claims 1, 4-7 and 18 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting an increased level of immunostaining on brain sections of $APP^{SW}xPS1^{M146L}$ transgenic mice or increased levels of antibodies against β-amyloid in serum and CSF samples of Alzheimer disease (AD) patients who are immunized with Aβ peptides,

AN1792(QS-21), and detecting a positive correlation between the increased immunostaining and improvement of immunization treatment in AD patients, does not reasonably provide enablement for a method of monitoring an immunotherapy in a subject suffering from Alzheimer's disease by contacting all types of test samples with all forms of amyloid plaque (including all fragments, derivatives or mutants) in all types of tissue sections and comparing the level of immunoreactivity to an undefined reference value of AD as broadly claimed."

In response, applicants respectfully traverse the Examiner's ground of rejection. Nevertheless, without conceding the correctness of the Examiner's rejection, applicants note that claim 1 has been amended hereinabove to recite that the immunoreactivity is detected on brain sections of $APP^{SW}xPS1^{M146L}$ transgenic mice in serum or CSF samples of Alzheimer's disease patients who are immunized with pre-aggregated Aβ1-42.

In view of this amendment, applicants maintain that the Examiner's ground of rejection has been rendered moot.

In view of the preceding remarks and the amendments to the claims, applicants maintain that claim 1 as amended and new claim 19 which depends therefrom satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection under 35 U.S.C. §112, first paragraph.

Rejections Under 35 U.S.C. §103

In section 8 at page 7 of the Final Office Action, the Examiner rejected claims 1, 4-7 and 18 under 35 U.S.C. §103 as allegedly not patentable over Dodel et al. (EP 1 172 378, published on January 16, 2002 as cited in the previous Office Action, hereinafter "Dodel") in view of Schenk et al. (Nature 400 (1999), 173-1779, hereinafter "Schenk").

In response, applicants respectfully traverse the Examiner's ground of rejection. Nevertheless, without conceding the correctness of the Examiner's rejection, applicants note that claim 1 has been amended hereinabove to recite that the immunoreactivity is detected on brain sections of $APP^{SW}xPS1^{M146L}$ transgenic mice in serum or CSF samples of Alzheimer's disease patients who are immunized with pre-aggregated Aβ1-42.

In this context, the Examiner is reminded that the same standard has to be applied for the assessment of the subject application and the cited prior art. Thus, when stating that the present application allegedly does not reasonably provide enablement for immunostaining on brain sections other than the mutant human APP and human Presenilin1 double-transgenic mice the same must apply to the prior art. Thus, the Schenk reference merely describing the mutant human APP (PDAPP) transgenic mice does not provide the person skilled in the art with enabling teaching for detecting an increased level of immunostaining on brain sections of the $APP^{SW}xPS1^{M146L}$ double-transgenic mice, let alone a reasonable expectation that those brain sections of a non-human animal could be used in a method of monitoring and prognosticating the clinical outcome of an immunotherapy in a human subject suffering from Alzheimer's disease and being immunized against pre-aggregated Aβ1-42.

This is all the more true in view of the fact that in accordance with the method of the present invention **human** antibody-containing serum and CSF sample are used to screen against an **animal**, i.e. mouse brain section and thus an immunoreactivity of components from different species.

Furthermore, the Examiner neglects the fact that besides Dodel fails to teach contacting serum or CSF with a brain section containing amyloid-plaques, wherein said brain section is derived from transgenic mice, in Dodel the level of anti-Aβ antibody is detected in samples from patients who have been passively immunized with human IgG immunoglobulins or anti-Aβ antibodies from human IgG rather than

immunized with Aβ1-42 as recited in the claim.

Furthermore, Dodel teaches "[t]he generation of naturally occurring Aβ-antibodies and subsequent Aβ / antibody complex formation, maybe involved in a normal clearance of Aβ peptide(s)"; see Dodel in column 3, section [0019], lines 42-45.

However, it is clear that the Aβ / antibody complex is formed with soluble Aβ. Thus, it would make no sense to screen for those antibodies which are supposed to form a complex with Aβ in human fluid in order to prevent Aβ deposition with brain tissue sections containing amyloid-plaques. This is all the more true in view of the fact that the epitopes recognized by the anti-Aβ antibodies taught in Dodel would be expected by the person skilled in the art to not match the epitopes that are accessible on the β-amyloid plaques present on the brain section.

Furthermore, contrary to the Examiner's assertion with reference to KSR International Co. v. Teleflex Inc. 82 USPQ2d 1385 (2007), plaque-containing brain sections of transgenic mice were not known to be suitable for the detection of protective human auto-antibodies against pre-aggregated Aβ1-42. The corresponding statement of the Examiner at page 9 of the Office Action that "[t]he detection of reduced amyloid plaques in immunized PDAPP mice as compared to non-immunized mice indicates that the antibodies generated from Abeta immunization can recognize amyloid plaques and thus there is a higher level staining in non-immunized mice" is based on hindsight assertion and not supported by Schenk. In particular, the Examiner asserts

> "Although Schenk does not directly use brain sections of non-immunized PDAPP mice to detect the levels of anti-Abeta antibodies in immunized mice, **it is expected to detect higher levels of amyloid-plaques on brain sections derived from non-immunized transgenic animals** and use as an indicator because the levels of anti-Abeta antibodies from patients or animals with Abeta immunization are

> increased in serum and CSF, **and can recognize the epitopes of Aß (immunogen) on the brain sections of non-immunized transgenic PDAPP animals** (amyloid-plaque containing tissue sections). Thus, the increased immunoreactivity as compared to prior to immunotherapy on brain sections containing human amyloid-plaques (PDAPP) is expected when contacted with the serum or CSF derived from animals or patients immunized with Abeta and thus to monitor the efficacy of immunotherapy. Accordingly, the claimed method as recited in instant claims are obvious over the applied references **because animals or patients immunized with Aβ generate anti-Aβ antibodies against Aβ plaques** and show reduced Aβ burden. Thus, a skilled artisan would have expected success in monitoring an immunotherapy in a subject suffering from AD by using brain sections of transgenic animals containing amyloid plaques as a tool to detect the anti-Abeta level after immunization because detection of higher levels of amyloid-plaques on brain sections of PDAPP mice is expected and the increased level of anti-Abeta antibodies in AD immunized with Abeta has been shown to reduce Abeta burden as taught by Schenk Dodel [*sic*], which is as an indicator of improvement of the immunotherapy in AD". *See* Office Action at pages 9 and 10 (emphasis added).

The assertion by the Examiner that "animals or patients immunized with Aβ generate anti-Aβ antibodies against Aβ plaques" is neither taught nor suggested in Schenk. Rather, Schenk states

> "Although it remains unproven, it is not unreasonable to expect that a similar reduction of neuropathology in AD patients would be of clinical benefit. Although our understanding of the precise aspects of the immune response that result in reduced pathology is incomplete, we have shown that $A\beta_{42}$ immunization results in the generation of anti-Aβ antibodies and that Aβ-immunoreactive monocytic/microglial cells appear in the regions of remaining plaques. Thus, one possible mechanism of action is that anti-Aβ antibodies facilitate clearance of amyloid-β either before deposition, **or** after plaque formation, by triggering monocytic/microglial cells to clear amyloid-β using signals mediated by Fc receptors". *See* Schenk at page 177, left column, third last full paragraph (emphasis added).

Thus, Schenk concludes that the anti-Aβ antibodies bind amyloid-β before deposition, i.e. plaque formation. Alternatively, Schenk

suggests that the anti-Aβ antibodies trigger monocytic/microglial cells to clear amyloid-β. There is no mentioning whatsoever that the anti-Aβ antibodies can recognize Aβ plaques on brain tissue, let alone that this could be an indicator for the success of immunotherapy.

Indeed, Schenk is acknowledged in Dodel in that way:

> Schenk and coworkers (Schenk et al, Nature 400:173, 1999) **investigated the plaque burden** in the PDAPP-mice following an immunization treatment. PDAPP-mice were immunised with pre-aggregated Aβ 20 for different time periods using Freud's adjuvans. **Plaque deposition in these mice decreased significantly** following the immunization treatment". *See* Dodel at 2, column 2, section [0008] (emphasis added).

Even Dodel being aware of the teaching of Schenk and as an inventor having skill above the average person skilled in the art has not envisaged that amyloid-plaque containing tissue sections of, for example, the transgenic PDAPP animals may be useful in monitoring an immunotherapy in a subject suffering from AD.

Rather, as stated by Dodel "[t]he goal is to **decrease β-amyloid concentration in the CSF and by that decrease the plaque burden** in Alzheimer's disease and alleviate the neuropsychiatric and neuropsychological defects in Alzheimer's disease. *See* Dodel in Example 1 at page 4, right column, lines 51-55 (emphasis added). Consequently, in Example 2 of Dodel, which is the only Example describing the effect of IgG immunoglobulin administration β-amyloid is measured in order to assess the efficacy of the treatment.

Thus, as acknowledged by the Examiner at page 11 and 12 of the Office Action assessing and determining the clinical outcome of immunotherapy of Aβ-immunization is taught by both Dodel and Schenk to be done by quantifying the amyloid-β burden and NOT by quantifying immunoreactivity on amyloid-plaque containing tissue sections.

Hence, since Dodel as well as Schenk propose that the anti-Aβ

antibodies exert the effect of lowering plaque burden by facilitating clearance and thus binding of Aβ in serum and CSF before plaque deposition, the skilled person would not have expected that the epitopes of soluble Aβ recognized by the anti-Aβ antibodies do not match the epitopes that are accessible on the β-amyloid plaques present on the brain section. Thus, it would make no sense to screen for those antibodies which are supposed to form a complex with soluble Aβ in human fluid in order to prevent Aβ deposition with brain tissue sections containing amyloid-plaques.

In summary, there is no indication in Schenk whatsoever that the antibodies generated from Aβ immunization can recognize amyloid plaques. Accordingly, it can also not be expected to detect higher levels of anti-Aβ antibodies on brain sections derived from the non-immunized transgenic animals, let alone that this would be an indicator for a successful therapeutic outcome. There is no teaching in Schenk that the anti-Aβ antibodies shown to be increased in serum and CSF can recognize the epitopes of Aβ on the brain sections of non-immunized transgenic PDAPP animals since, as mentioned, Schenk as well as Dodel teach and suggest that the generated anti-Aβ antibodies prevent plaque formation beforehand.

Furthermore, contrary to the Examiner's assertion at page 11 and 12 of the Office Action Schenk does NOT teach a positive correlation of the level of anti-Aβ antibodies in serum and CSF after treatment or immunization with Aβ. Schenk states:

> "We found that eight of nine PDAPP mice immunized with Aβ42 developed and maintained serum antibody titres against Aβ42 of greater than 1:10,000. The ninth mouse had a lower titre, of approximately 1:1,000.
>
> ...
>
> Immunization with Aβ42 resulted in almost complete prevention of amyloid-β deposition (Figs 1, 2). Seven of nine mice immunized with Aβ42, including the mouse with

> the lowest anti-Aβ titre, had no detectable amyloid-β deposits in their brains. One mouse from this treatment group had a single isolated plaque in the six brain sections examined, whereas a second animal had a greatly reduced amyloid-β burden". *See* Schenk at page 174, left column, third last full sentence and right column, lines 4-10 (emphasis added).

Hence, a mouse having an anti-Aβ antibody titre of more a magnitude less than the mean performed as good as the mice having high titres and even better than two of those. Thus, according to the observation by Schenk the level of anti-Aβ antibodies does not indicate the outcome of neuropathology in terms of Aβ burden and amount of plaque deposits in the brain. Hence, for the second series of experiments described at page 176 Schenk confined its analysis to the examination of Aβ burden similarly as Dodel in its Example 2.

However, as discussed in the present application and meanwhile acknowledged in the art determining the level of Aβ does also not allow any conclusion as to the significance of this observation for the clinical outcome of the therapy of patients suffering from Alzheimer's disease.

Indeed, this is one significant shortcoming of the method of monitoring immunotherapy taught in Dodel and Schenk because of which applicants' contribution to the art has been acknowledged in the field of Alzheimer's disease to represent "an important step forward to ultimately treat this intractable disease"; see Sambamurti et al. at page 176, right column, last sentence. Certainly, the skilled person could not have expected that immunized patients with unchanged plasma and CSF level of Aβ, when scored positive in the TAPIR assay of the claimed invention clinically improved and even performed better than patients having high ELISA titers; see the specification at page 19, the bridging paragraph to page 20 and the last paragraph at that page.

For the reasons stated above, applicants maintain that Dodel et al. in view of Schenk et al. 1999 or Schenk (US'523) do not render obvious applicants' claimed invention.

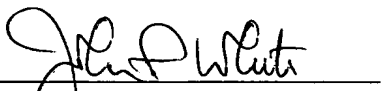
In view of these remarks, applicants maintain that claim 1 as amended and the claims which depend therefrom, satisfy the requirements of 35 U.S.C. §103. Accordingly, applicants respectfully request the Examiner reconsider and withdraw this ground of rejection.

Summary

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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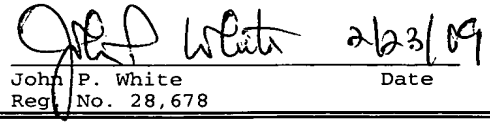

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